

Use of thyroglobulin as a tumour marker

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Author contributions: Indrasena BSH performed the whole of the writing.

Conflict-of-interest statement: None.

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Manuscript source: Invited manuscript

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Received: September 28, 2016

Peer-review started: October 7, 2016

First decision: November 10, 2016

Revised: December 28, 2016

Accepted: January 11, 2017

Article in press: January 14, 2017

Published online: February 26, 2017

Abstract

It is worthwhile to measure serum thyroglobulin (TG) level in thyroid cancer before subjecting patients to surgery for two reasons. Firstly, if the level is high, it may give a clue to the local and metastatic tumour burden at presentation; secondly, if the level is normal,

it identifies the patients who are unlikely to show rising TG levels in the presence of thyroid cancer. Those who have high serum TG before surgery will show up recurrence as rising serum TG during the postoperative period. Those who do not have high serum TG before surgery will not show up rising serum TG in the presence of recurrent disease. In the latter situation, normal TG level gives only a false reassurance regarding recurrence of disease. Nevertheless, rising serum TG during the postoperative period must be interpreted cautiously because this could be due to the enlargement of non-cancerous residual thyroid tissue inadvertently left behind during surgery.

Key words: Thyroglobulin; Thyroid cancer; Recurrent thyroid cancer; Anti-thyroglobulin antibodies; Tumour marker

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Core tip: Although serum thyroglobulin (TG) is widely used as a tool to detect recurrence of thyroid cancer, it is widely held that preoperative TG measurement is unnecessary. It is true that preoperative TG level is hardly of much diagnostic value, but without a preoperative TG report, it is not possible to safely utilize serial serum TG subsequently as a monitoring tool. Routine measurement of serum TG before surgery is, therefore, recommended.

Indrasena BSH. Use of thyroglobulin as a tumour marker. *World J Biol Chem* 2017; 8(1): 81-85 Available from: URL: <http://www.wjgnet.com/1949-8454/full/v8/i1/81.htm> DOI: <http://dx.doi.org/10.4331/wjbc.v8.i1.81>

INTRODUCTION

Serial measurement of thyroglobulin (TG) is being practised by many clinicians to detect recurrence of thyroid cancer after surgery^[1-3]. Apart from that, there is hardly

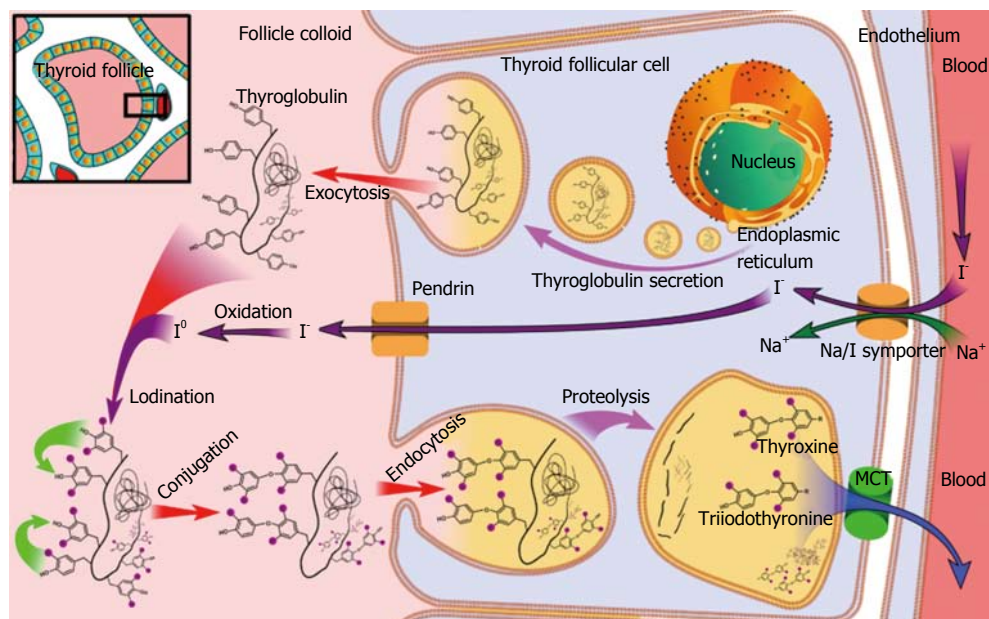


Figure 1 Metabolism of thyroglobulin^[20].

any use of TG as a diagnostic modality of thyroid cancer because it is not tumour specific^[4]. The serum level of TG reflects the thyroid tissue burden in the body regardless of underlying pathology whether benign or malignant. Since the serum levels are proportional to the volume of thyroid tissue, it can be used successfully to evaluate the "cancer burden" at presentation as well as to assess the adequacy of surgery, monitor the recurrences and progression of disease before and after cancer treatment. Its use as a monitoring tool is only valid provided certain precautions are seriously taken into account. Otherwise, false reassurance is inevitable in the presence of on going disease.

BIOCHEMISTRY

TG is a glycoprotein molecule synthesised exclusively by the thyroid follicular cells. These are stored as colloid within the thyroid follicles, iodinated and degraded to thyroxine and tri-iodothyronine. The whole process is regulated by thyroid stimulating hormone (TSH) (Figure 1).

TG in serum has a half-life of 65 h^[5]. The serum level TG is proportional to the volume of thyroid tissue in the body at a rate 1 ng/mL per 1 g of thyroid mass. Since the size of the normal thyroid gland is 20-25 g, the reference range has to be generally about 20 to 25 ng/mL. However, the normal serum TG level depends on the gender and the level of iodine intake of the patient. The gender specific reference range has been given as 1.40-29.2 ng/mL for males and 1.50-38.5 ng/mL for females^[6]. In countries with iodine deficiency the reference range may be higher^[7,8]. This is because of elevated TSH in serum in the presence of iodine deficiency; TSH stimulates the thyroid follicular cells to synthesise more TG. Apart from gender and iodine

intake, the measured TG level is also influenced by autoantibodies against TG (anti-TGAb), cigarette smoking and TSH status unrelated to iodine intake. The measured serum TG levels are masked by the presence of anti-TGAb in blood. Anti-TGAb bind to the TG molecules masking the epitopes on the TG molecule to which the antibodies of the radio immuno assay (RIA) test bind. As a result, the measured TG level by RIA in such patients, will be falsely low. Anti-TGAb can be seen in cases of Hashimoto's disease, Graves' disease, 20% of patients with thyroid carcinoma^[9], and 10% of normal population without any thyroid disease^[10].

CLINICAL USES OF TG

Evaluation of completeness of surgery

TG can be elevated in any thyroid pathology. Serum TG level is proportional to the thyroid mass rather than the type of pathology^[8]. As a guide, one gram of normal thyroid tissue is equivalent to 1 ng/mL of TG in serum in euthyroid state; in a TSH suppressed state, this is equivalent to 0.5 ng/mL. After total thyroidectomy, theoretically, the level has to drop to zero because no thyroid tissue is expected to leave behind after total thyroidectomy. Persistent presence of TG after total thyroidectomy, even at low concentrations, points to the possibility of inadequate surgery leading to residual thyroid tissue at the thyroid bed (in the absence of local or distant metastases). After hemithyroidectomy, the preoperative level should theoretically drop to 50% of preoperative value. After near total thyroidectomy, *i.e.*, total lobectomy on one side plus isthmusectomy plus subtotal lobectomy on the other side (leaving behind overall 1/8th of the size of a normal sized gland weighing 25 g), a TG level of 3-4 ng/mL can be expected to

present in serum when TSH is normal, and 1.5-2 ng/mL when TSH has been suppressed with high doses of thyroxine.

The serum TG level post surgery reflects the amount of residual thyroid mass. In the absence of metastatic disease, this reflects the size of the thyroid remnant left behind during surgery. Since TG has a half-life close to 3 d, it can be shown that the TG level has to be less than 0.5 ng/mL at the end of three weeks after total or near total thyroidectomy for a goitre of a size of three times normal. This can be used as a guide to initiate radio active iodine treatment for remnant ablation, the residual thyroid mass being as a result of inadequate surgery or metastatic disease. However, although such a hypothesis carries high positive predictive value, a negative result does not reliably exclude the possibility of residual disease. The TG serum level at 3 wk post surgery not only depends on the residual thyroid mass but also the size of the gland at the time of surgery as well as TG producing capacity of the tumour.

As a monitoring tool

TG can be secreted by differentiated cancer cells of the thyroid. This includes nearly two thirds of differentiated thyroid cancers (follicular neoplasms, all papillary carcinomas, Hurthle cell tumours of the thyroid), up to 50% of poorly differentiated and anaplastic carcinomas of thyroid and some medullary carcinomas. The cancerous nodules can be stained with immunohistochemical methods to specifically demonstrate TG. TG has been demonstrated in cancerous follicles both in the thyroid as well as in metastatic deposits in lymph nodes and elsewhere.

The use of TG as a screening and diagnostic tool of differentiated thyroid cancer is poor (Sensitivity and specificity is 70% and 80% respectively for follicular carcinoma) because both benign and malignant thyroid glands secrete TG^[11]. Elevated TG levels can be seen in benign conditions like Graves' disease and thyroiditis, as well as in thyroid cancer. Further, there is a subset of thyroid cancer patients (12%) whose TG level is low or low-normal as opposed to a minority whose blood level is very high (> 1000 ng/mL). A level > 5000 ng/mL is indicative of metastatic disease^[12]. Patients who develop cancer as a result of mutations of TG gene may not express TG even though they have a hypothyroid goitre (high TSH) as well as cancer^[13].

Those who have high serum TG one month after thyroidectomy are more likely to develop cancer recurrence, the value being proportional to the burden of remaining metastatic disease^[14]. However, high serum TG could be due to distant metastatic disease or incomplete excision of the gland during thyroidectomy. Holsinger *et al*^[15] reported that 57% of patients who were supposed to have had total thyroidectomy for thyroid cancer had residual thyroid tissue at the thyroid bed when tested by postoperative radioactive iodine uptake test. Therefore, the surgeon must be sure that the whole thyroid gland has been removed before utilizing TG as a prognostic indicator. Or else the patient must have undergone

remnant ablation with radioactive iodine before TG testing.

TG has been used frequently to monitor recurrent disease after thyroidectomy. Not only the first recurrence but also subsequent recurrences can be detected by monitoring serum TG level. The TG level has to be done every 6 to 12 mo. However, certain points need to be kept in mind when utilizing TG alone as a tumour marker to detect recurrence. TG can rise after thyroidectomy when the residual thyroid gland enlarges even though it does not harbour malignant cells. This could happen after near total thyroidectomy (total lobectomy on one side plus isthmusectomy plus subtotal lobectomy on the other side) when about 4 g of the gland is left behind purposely on one side, or glandular tissue left behind inadvertently in the neck because of difficult thyroidectomy. In such instances, serum TG could give false positive result. Therefore, more often than not, surgeons prefer to subject all patients to remnant ablation therapy after thyroidectomy for cancer. Such patients are more suitable for monitoring by TG than otherwise.

It may not be able to see high serum TG after thyroidectomy if the TG level before surgery had been low or normal. Therefore, it is necessary to recognise patients who would not have rising TG in the presence of recurrence before using TG as a tumour marker. This can only be done if the serum TG level before the surgery is known. Those who have normal or low serum TG before surgery will not show rising serum TG when there is recurrence of disease^[16]. This happens irrespective of the anti-TGAb status of the patient^[17]. Such patients must be offered iodine scintigraphy to detect recurrence. Furthermore, there is a possibility of transforming a differentiated thyroid cancer to anaplastic variety over time^[18]. In such a case, TG will not rise in the presence of recurrence.

PRECAUTIONS

It may take nearly one month (7 to 10 $t_{1/2}$) for the TG to disappear from the circulation after total thyroidectomy in the absence of metastases^[5].

Since there is a theoretical possibility of releasing TG in to the circulation following trauma, it would be a valid precaution to measure TG before FNAC test or 2 wk after FNAC, although there are no references to strongly recommend this approach.

In postoperative patients, thyroxine must preferably be stopped at least six weeks before the measurement of serum TG if the patient has been on thyroxine or two weeks before if the patient has been on liothyronine (tri-iodothyronine). The idea is to allow TSH level to rise from the suppressive levels to higher levels making the residual cancer tissue to synthesise and secrete TG stimulated by TSH. This is also the standard practice in postoperative use of radioactive iodine for diagnostic and therapeutic purposes. Alternatively, to minimize the risks associated with stopping thyroxine for six weeks, thyroxine can be stopped only for three weeks before the TG test,

Table 1 Interpretation and management of different serum thyroglobulin values

Stage of disease	Serum TG level			Uses and further action
	Low	Normal	Elevated	
Before surgery	Anti-TGAb or TG non-secreting tumour			TG can not be used subsequently to monitor disease activity
3-4 wk after surgery	Anti-TGAb, successful local surgery or no metastatic disease	Benign or malignant thyroid disease		TG can be used subsequently to monitor disease activity
		Incomplete local surgery, metastatic disease or recurrence		Do 125-Iodine scan to screen for residual local disease and distant metastases
Long term follow-up	Anti-TGAb Cure or stable disease	Recurrence or progression		Remnant ablation therapy (131-Iodine or further surgery) is indicated
				Do other tests to monitor disease activity Disease activity can be monitored by periodic TG measurements Further investigations and treatment

TG: Thyroglobulin; anti-TGAb: Autoantibodies against TG.

but the test may have to be repeated after six weeks of cessation of thyroxine if TG and TSH are normal^[19]. Another alternative is to stop thyroxine six weeks before and to put the patient on liothyronine for four weeks and do the test two weeks later after stopping liothyronine. Liothyronine has a shorter half-life than thyroxine. Recombinant human TSH can also be used, instead, to stimulate residual thyroid tissue without stopping thyroid suppression treatment.

CONCLUSION

Interpretation of serum TG measurements could be a quite complex task. It may be elevated in both benign and malignant disease of the thyroid gland. Therefore, its use as a diagnostic tool of cancer is negligible. TG level 3-4 wk post surgery can be used to assess the size of the residual thyroid mass either locally or distally, and guide remnant ablation therapy. Rising levels in the postoperative period could happen due to progression of cancer or growth of residual thyroid tissue at the thyroid bed following inadequate surgery. It may remain normal in malignant thyroid disease both pre and post operatively due to non-secreting varieties of thyroid cancer or due to the presence of anti-TGAb in serum, and such cases could only be detected by checking TG levels before surgery.

The changes of TG that can be expected at different stages of the disease and how different TG levels assist in decision making and the management of thyroid cancer has been summarised in Table 1.

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P- Reviewer: Salvatore B, Shi YF, Xie L **S- Editor:** Song XX

L- Editor: A **E- Editor:** Li D





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